

Bipolar disorder risk alleles in children with ADHD

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Abstract Bipolar disorder (BD) and attention deficit/hyperactivity disorder (ADHD) may share common genetic risk factors as indicated by the high co-morbidity of BD and ADHD, their phenotypic overlap especially in pediatric populations, the high heritability of both disorders, and the co-occurrence in families. We therefore examined whether known polygenic BD risk alleles are associated with ADHD. We chose the eight best SNPs of the recent genome-wide association study (GWAS) of BD patients of German ancestry and the nine SNPs from international

GWAS meeting a ‘genome-wide significance’ level of $\alpha = 5 \times 10^{-8}$. A GWAS was performed in 495 ADHD children and 1,300 population-based controls using HumanHap550v3 and Human660 W-QuadV1 BeadArrays. We found no significant association of childhood ADHD with single BD risk alleles surviving adjustment for multiple testing. Yet, risk alleles for BD and ADHD were directionally consistent at eight of nine loci with the strongest support for three SNPs in or near *NCAN*, *BRE*, and *LMAN2L*. The polygene analysis for the BP risk alleles at all 14 loci indicated a higher probability of being a BD risk allele carrier in the ADHD cases as compared to the controls. At a moderate power to detect association with ADHD, if true effects were close to estimates from GWAS for BD, our results suggest that the possible contribution of BD risk variants to childhood ADHD risk is considerably

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lower than for BD. Yet, our findings should encourage researchers to search for common genetic risk factors in BD and childhood ADHD in future studies.

Keywords Mood disorder · Genome-wide association study · Genetics · Childhood · Adolescence

Introduction

Differential diagnosis of bipolar disorder (BD) in pediatric populations is difficult due to its overlap with disruptive behavior disorders such as attention deficit/hyperactivity disorder (ADHD; Holtmann et al. (2010) in Bipolar Disorder). In adults with BD, almost 20 % met criteria for lifetime ADHD (McIntyre et al. 2010), in adolescents with BD this rate was more than 70 %, and in prepubertal BD as high as 98 % (Geller et al. 2000). The controversial discussion as to the existence of pediatric BD led to the proposal of a ‘temper dysregulation with dysphoria’ (TDD) category to be included into the mood disorder section of DSM-V (APA; www.dsm5.org). The proposed TDD criteria are highly congruent with those of the earlier defined ‘severe mood dysregulation’ syndrome (Leibenluft et al. 2003), and approximately 85 % of youth with severe mood dysregulation meet criteria for ADHD (APA; www.dsm5.org). Thus, it is likely that pediatric BD and ADHD share some common genetic risk factors.

Recently, Landaas et al. (2011) as well as Weber et al. (2011) examined whether relevant BD single nucleotide polymorphisms (SNP) derived from BD genome-wide association studies (GWAS) were associated with adulthood ADHD. Landaas and colleagues found no evidence for an association in 561 Norwegian adults with ADHD, while Weber and colleagues found evidence for association

of a haplotype in the diacylglycerol kinase gene (*DGKH*) with BD, adulthood ADHD ($n = 535$) and unipolar depression. Their studies were based on the assumptions that both ADHD and BD were highly heritable, often co-occurred in families (Birmaher et al. 2010), partly overlapped in phenotype, i.e., impaired impulse control, dysregulation of energy/activity level as well as mood instability (Skirrow et al. 2009), and frequently co-occurred in adults (Wingo and Ghaemi 2007), and thus likely to share some common genetic risk factors. Yet, adulthood ADHD represents only a subgroup of the childhood ADHD population, whose symptoms persists into adulthood (40–50 %; Kessler et al. 2010).

Recently, Cichon et al. (2011) conducted a GWAS in 682 patients with BD and 1,300 controls, both groups of German ancestry, and replicated their results in samples of European ancestry summing up to 2,411 BD patients and 3,613 controls. The primary aim of our current study was to examine whether the best eight single nucleotide polymorphism (SNPs) alleles found to be associated with BD by Cichon et al. (2011) were also associated with childhood ADHD in a sample of 495 ADHD children of similar ancestry. The secondary aim was to assess the association of SNP alleles with childhood ADHD, which were found to be genome-wide significant for BD in international GWAS (at $p < 5 \times 10^{-8}$).

Materials and methods

Samples

The sample is based on a GWAS for childhood ADHD ($n = 495$; Hinney et al. 2011). As the control sample of our GWAS was the same as the one used by Cichon et al. [(2011); controls 1], we re-analyzed our association results for these SNPs using a second, independent control sample (controls 2).

ADHD cases

Four hundred and ninety five children and adolescents with ADHD (age range 6–18 years) were recruited and phenotypically characterized in six psychiatric in- and outpatient units for children and adolescents (Aachen, Cologne, Essen, Marburg, Regensburg, and Würzburg). Patients were included if they were diagnosed with ADHD according to DSM-IV (American Psychiatric Association 1994); the subtypes are given in Table 1. The ascertainment strategy and inclusion criteria have been described previously (Hinney et al. 2011; Hebebrand et al. 2006; Schimmelmann et al. 2007). The socio-demographic and diagnostic characteristics of the 495 children with ADHD are displayed in Table 1.

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Table 1 Clinical characteristics of children with ADHD ($n = 495$)

	Probands n (%) or mean (SD)
Sex	
Male	400 (80.8 %)
Female	95 (19.2 %)
Age	11.00 (SD 2.7)
Subtypes ^a	
Predominantly inattentive	108 (21.8 %)
Predominantly hyperactive-impulsive	25 (5.1 %)
Combined	362 (73.1 %)
Comorbidities ^{a,b}	
Oppositional defiant disorder	167 (35.0 %)
Conduct disorder	56 (11.6 %)
Mood disorders likely ^c	42 (8.7 %)
Anxiety disorders likely ^d	191 (39.6 %)

^a Current DSM-IV diagnosis according to K-SADS, Kinder-DIPS or PACS

^b Multiple scoring possible; information for 13 patients was missing (i.e., 100 % pertain to $n = 482$)

^c Diagnoses: major depressive disorder or dysthymic disorders according to K-SADS/Kinder-DIPS, or mood disorder likely according to PACS

^d Diagnoses: generalized anxiety disorder, separation anxiety disorder, social phobia, specific phobias according to K-SADS/Kinder-DIPS or anxiety disorder likely according to PACS

Controls 1

Thousand three hundred controls of German ancestry met the quality control criteria (for details see Cichon et al. 2011); the control individuals were drawn from three German population-based epidemiological studies: (a) the Heinz Nixdorf Recall (Risk Factors, Evaluation of Coronary Calcification, and Lifestyle) study ($n = 383$; Schmermund et al. 2002), (b) PopGen ($n = 490$; Krawczak et al. 2006), (c) KORA ($n = 488$; Wichmann et al. 2005). The recruitment areas were Essen, Bochum, and Mülheim (Ruhr area) for (a), Schleswig-Holstein (Northern Germany) for (b) and Augsburg (Southern Germany) for (c), respectively.

Controls 2

A second independent sample of 1,133 controls of German ancestry was derived from the population-based epidemiological Heinz Nixdorf Recall study (Schmermund et al. 2002). The results pertaining to Control 2 for the markers reported in Cichon et al. (2011) are provided in a supplementary Table.

Written informed consent was given by all participants and in case of minors by their parents. Studies were

approved by the respective institutional review boards or ethics committees and conducted in accordance with the *Declaration of Helsinki*.

SNP selection and genotyping

For the primary aim, we chose the eight best SNPs tagging seven loci associated with BD according to the combined analysis of Cichon et al. (2011), i.e., rs6547829, rs779279, rs10278591, rs11764590, rs985409, rs2209263, rs9322993, and rs1064395. For the secondary aim, we chose nine SNPs tagging another seven loci from the meta-analysis by Chen et al. (2013): rs6746896 in *LMAN2L*, rs7618915 at chromosome 3p21, rs9834970 in *TRANK1*, and 4948418 in *ANK3*; from the GWAS by Ferreira et al. (2008) supported by the meta-analysis by Liu et al. (2011): rs10994336 and rs1938526 in *ANK3*; from the GWAS by Sklar et al. (2011): rs12576775 in *ODZ4* and rs4765913 in *CACNA1C*; and from the GWAS by Baum et al. (2008): rs1012053 in *DGKH*.

The original GWAS analysis was performed using the 495 ADHD children and 1,300 controls (controls 1 sample; see Hinney et al. 2011). Genome-wide genotyping was performed on HumanHap550v3 and Human660 W-QuadV1 BeadArrays (Illumina, San Diego, CA, USA) by (i) Illumina's customer service, San Diego, CA, USA (all PopGen controls); (ii) the Department of Genomics, Life and Brain Center, University of Bonn, Germany (all ADHD cases and Heinz Nixdorf Recall study controls) and (iii) the Helmholtz Zentrum, München, Germany (all KORA controls). We applied a quality control (QC) protocol to filter genotypes and individuals to the overlapping genotype content of all GWAS data sets. This QC protocol has been previously described in detail (Hinney et al. 2011). It accounts for call rates (CR—cutoff 0.98 for SNPs and 0.97 for individuals), heterozygosity, cross-contamination, population stratification, relatedness, deviations from Hardy–Weinberg equilibrium (HWE—cutoffs $p_{\text{exact-cases}} < 1 \times 10^{-6}$, $p_{\text{exact-controls}} < 1 \times 10^{-4}$) and minor allele frequencies (MAF—cutoff < 1 % in cases or controls). Moreover, we explored the cluster intensity plots of the SNPs that were followed up manually by two independent raters.

Statistical analysis

Genotype distributions in both ADHD cases and each of the two control samples were tested for departure from Hardy–Weinberg equilibrium by an exact test (all $p > 0.01$ except for rs12576775 where the exact two-sided p value was 0.001, highlighted by footnote (e) in Table 2). We applied logistic regression with (log-)additive allele coding to the BP SNPs and report nominal two-sided p values based on Wald-type

Table 2 Frequencies of BD risk alleles in ADHD patients and controls (controls 1)

Chromosome gene locus	SNP (proxy, r^2) ^a	Minor allele (A)	Frequency risk allele/genotype frequencies (AA/AB/BB)		OR (95 % CI) for minor allele	$p^{\text{a, b}}$	OR from literature for minor allele ^{b, c}	References
			ADHD patients	Controls				
2 <i>BRE</i>	rs6547829	T	0.09 2/89/404	0.07 6/167/1127	1.41 (1.08–1.84)	0.011	1.32	Cichon et al. (2011)
3 <i>FGF12</i> ; <i>PYDC2</i>	rs779279	A	0.47 106/251/ 138	0.48 287/667/ 336	0.95 (0.82–1.10)	0.468	0.86	Cichon et al. (2011)
7 <i>MAD1L1</i>	rs10278591	T	0.22 21/177/297	0.21 60/420/820	1.08 (0.91–1.29)	0.376	1.21	Cichon et al. (2011)
	rs11764590	T	0.21 19/174/302	0.20 58/409/831	1.08 (0.90–1.28)	0.431	1.26	Cichon et al. (2011)
7 <i>LHFPL3</i>	rs985409	G	0.42 90/231/167	0.38 194/610/ 496	1.17 (1.00–1.35)	0.044	1.17	Cichon et al. (2011)
9 <i>TLE4</i> ; <i>TLE1</i>	rs2209263	A	0.26 39/182/274	0.30 120/545/ 635	0.83 (0.70–0.97)	0.022	0.84	Cichon et al. (2011)
14 <i>SIP1</i>	rs9322993	T	0.07 3/59/433	0.04 5/104/1191	1.51 (1.10–2.05)	0.009	1.37	Cichon et al. (2011)
19 <i>NCAN</i>	rs1064395	A	0.16 12/133/350	0.14 34/285/981	1.19 (0.97–1.45)	0.087	1.31	Cichon et al. (2011)
2 <i>LMAN2L</i>	rs6746896	G	0.33 48/232/215	0.37 179/610/ 511	0.83 (0.71–0.97)	0.021	NA ^d , BD risk allele A	Chen et al. (2013)
3 <i>3p21</i>	rs7618915 (rs13094687, 0.96)	G	0.37 64/238/193	0.37 174/608/ 518	1.01 (0.87–1.18)	0.911	NA ^d , BD risk allele G	Chen et al. (2013)
3 <i>TRANK1</i>	rs9834970 (rs1553656, 0.82)	T	0.46 103/251/ 141	0.46 267/665/ 368	1.00 (0.86–1.16)	0.980	NA ^d , BD risk allele C	Chen et al. (2013)
10 <i>ANK3</i>	rs4948418	T	0.07 0/70/428	0.07 7/167/1125	1.01 (0.75–1.34)	0.913	NA ^d , BD risk allele T	Chen et al. (2013)
	rs10994336 (rs10994397, 1.00)	T	0.07 0/68/427	0.07 7/158/1135	1.04 (0.77–1.39)	0.785	1.45	Ferreira et al. (2008)
	rs1938526	C	0.07 0/72/423	0.07 8/163/1129	1.06 (0.79–1.41)	0.683	1.40	Ferreira et al. (2008)
11 <i>ODZ4</i>	rs12576775 ^e	G	0.17 11/143/341	0.17 21/399/880	0.98 (0.80–1.20)	0.826	1.14	Sklar et al. (2011)
12 <i>CACNA1C</i>	rs4765913 (rs4765914, 0.87)	T	0.19 17/155/323	0.19 40/413/846	1.01 (0.83–1.22)	0.937	1.14 ^f	Sklar et al. (2011)
13 <i>DGKH</i>	rs1012053	C	0.15 12/123/360	0.16 29/355/907	0.92 (0.74–1.12)	0.396	0.63	Baum et al. (2008)

ANK3 ankyrinG; *BRE* brain and reproductive organ expressed; *CACNA1C* calcium channel, voltage dependent, L type, alpha 1C subunit; *DGKH* diacylglycerol kinase, eta; *FGF12* fibroblast growth factor 12; *LHFPL3* lipoma HMGIC fusion partner-like 3; *LMAN2L* lectin, mannose-binding 2-like; *MAD1L1* MAD1 mitotic arrest deficient-like 1; *NCAN* neurocan; *ODZ4* odd Oz/ten-m homolog 4 (Drosophila); *PALB2* partner and localizer of BRCA2; *PYDC2* pyrin domain containing 2; *SIP1* survival of motor neuron protein interacting protein 1; *TLE1/TLE4* transducin-like enhancer of split 1/4; *TRANK1* tetratricopeptide repeat and ankyrin repeat containing 1; *CI* confidence interval; *NA* not applicable; association signals with nominal p values below 5 % in bold

^a r^2 based on 1000 Genomes Pilot 1; results are those reported for the proxy in case a proxy is provided

^b Nominal two-sided p values

^c For the originally reported SNP—switched to the minor allele effects where necessary by (1/OR)

^d No OR reported by Chen et al. 2013; however, the BP risk allele was available

^e Evidence for a violation of the Hardy–Weinberg equilibrium assumption exact p value (two-sided) in controls 0.001

^f For the original SNP rs4765913 the minor allele A was the BD risk allele

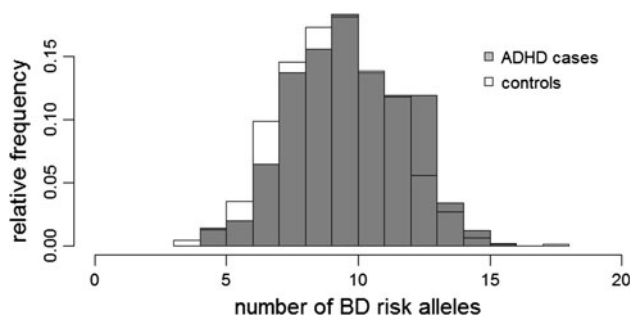


Fig. 1 Overlaid histograms of the number of BD risk alleles (possible range from 0 to 28) in ADHD patients and controls (controls 1)

test statistics. The comparison-wise significance level α after correction for multiple testing was set at 0.0035 ($<0.05/14$, with 14 being the total number of loci tested). We used QUANTO (<http://hydra.usc.edu/GxE>) for power calculation. The power was calculated for a level α of 0.0035 (two-sided) under a (log-)additive inheritance mode for minor allele frequencies between 4 and 50 % resembling those reported in the original studies (see Table 2). In the absence of risk allele effects for ADHD, we used an average effect size of 1.50, given that effect sizes for BP risk allele effects ranged from 1.14 to 2.08 (see Table 2). For a sample size of 495 ADHD cases and 1,300 controls, the power ranged between ~30 and 99 % for all tests. Thus, our study is sufficiently powered to detect larger genetic effects for more frequent variants. In addition to single SNP analyses, we compared the risk alleles for directional consistency by one-sided binomial sign tests and explored a polygenic score by counting the unweighted number of BD risk alleles for each of the 14 loci (for multiple SNPs per locus we randomly selected one of them). The BD risk score was subsequently plotted as overlaid histogram for ADHD cases and controls (controls 1; see Fig. 1). Both BD risk score distributions were compared using the two-sided Wilcoxon–Mann–Whitney (WMW) test.

Results

Association study for BD risk alleles in ADHD

The results of the association analysis between BD risk SNPs and childhood ADHD are displayed in Table 2. ORs and nominal p values are reported. For comparison, the odds ratios for the minor alleles reported in the original BD GWAS are also listed. For the SNPs by Cichon et al. (2011), a separate table with a comparison to an independent control group (controls 2) has been included (supplementary Table 1).

In detail, focusing on the BD SNP risk alleles reported by Cichon et al. (2011), we detected evidence for an

association to ADHD with uncorrected p values of <0.05 for four SNPs when using the same controls as those used by Cichon et al. (2011). In all these cases, the BD risk alleles matched those associated with ADHD. None of these association results survived control for multiple testing (at $\alpha = 0.0035$), and none of the findings using the second control sample (controls 2) met nominal significance again (supplementary Table 1). Only for the two coding SNPs in *NCAN* and *BRE*, we observed a consistent risk allele pattern across both control group comparisons (rs1064395 in *NCAN*: $OR_{combined} = 1.20$, 95 % confidence interval (0.99–1.44); rs6547829 in *BRE*: $OR_{combined} = 1.34$, 95 % confidence interval (1.05–1.70)). Regarding the BD susceptibility SNPs of the other BD studies, our analyses revealed suggestive evidence for association with ADHD in rs6746896 near *LMAN2L* (Chen et al. 2013; uncorrected p value 0.021) and no evidence for association with ADHD for the remaining eight SNPs, which were found to be genome-wide significant for BD in international GWAS (at $\alpha = 5 \times 10^{-8}$; Baum et al. 2008; Chen et al. 2013; Ferreira et al. 2008; Liu et al. 2011; Sklar et al. 2011).

Directional effects and polygene BP risk score analysis

For seven of the eight SNPs implicated in BD by Cichon et al. (2011), it was possible to compare the direction of BD effect alleles and (potential) ADHD risk alleles. For six of these seven SNPs (5/6 loci), we detected directionally consistent effects on the risk of ADHD irrespective of the controls used (one-sided binomial sign test, $p_{loci} = 0.02$). The remaining one SNP (rs779279) was not assessed because the ADHD risk allele effect was smaller than 1.05 (indicating uncertain direction of effect). Altogether, for nine of ten SNPs (8/9 loci) reported by Baum et al. (2008), Chen et al. (2013), Cichon et al. (2011), Ferreira et al. (2008), and Sklar et al. (2011), we detected directionally consistent effects on the risk of ADHD (one-sided binomial sign test, $p_{loci} = 0.002$). Including the single SNP by Cichon et al. (2011) mentioned above, seven SNPs were not assessed because the ADHD risk allele effect was smaller than 1.05. Figure 1 displays the overlaid histograms of the BD polygene risk score for ADHD cases and controls (controls 1). The median number of BD was ten for ADHD cases (1st quartile: 9; 3rd quartile: 12) and ten for the controls (1st quartile: 8; 3rd quartile: 11), respectively. Overall, ADHD cases had a higher probability of being a BD risk allele carrier as compared to the controls ($p_{WMW} = 6.42 \times 10^{-5}$).

Discussion

Clinical evidence has accumulated for potentially shared genetic risk factors in BD and ADHD. Accordingly, we

hypothesized that the BD risk alleles found in genome-wide association studies, particularly in the GWAS by Cichon et al. (2011) in a sample of comparable ancestry, were relevant for the ADHD phenotype. We re-analyzed our findings using a second independent control sample, as our initial controls were identical with the control sample in Cichon et al. (2011). We found no significant association of childhood ADHD with BD risk alleles surviving validation in a second independent control sample or adjustment for multiple testing. However, in three coding SNPs in *NCAN*, *BRE* and in one near *LMAN2L*, risk allele patterns in BD were consistent with those observed for ADHD. Notably, rs1064395 in *NCAN* was the only SNP fulfilling the genome-wide significance criterion of $\alpha = 5 \times 10^{-8}$ in the study by Cichon et al. (2011). We detected that the risk alleles for BD and ADHD were directionally consistent in eight out of the nine loci identified in the study by Cichon et al. (2011) and all other BP studies. Moreover, the polygene analysis for the BP risk alleles at all 14 loci indicated a higher probability of being a BD risk allele carrier in the ADHD cases as compared to the controls.

Generally, large sample size and replication are mandatory in genetic studies to minimize the risk of false positive or negative findings (Albayrak et al. 2008). Our study has relatively good power to detect an association with ADHD, if the true effects are close to the estimates from the GWA studies for BD. However, the study is clearly underpowered to detect small to moderate effects for lower MAFs. For example, focusing an OR of 1.3, all other aspects held constant, leads to a range from 7 % (for a MAF of 4 %) to 72 % (for a MAF of 50 %). Thus, while our results suggest that the possible contribution of BD genes to the risk of childhood ADHD is probably considerably lower than for BD, the findings at least justify further studies in larger samples on the putative shared genetic risk factors of BD and childhood ADHD including genome-wide comparisons using a polygene approach as recently shown in Berndt et al. (2013).

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Conflict of interest The authors declare that they have no conflict of interest relevant to this work.

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